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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,299	10/09/2001	Yoshiya Gunji	212289US0PCT	4922

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EXAMINER

STEADMAN, DAVID J

ART UNIT PAPER NUMBER

1652

DATE MAILED: 07/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,299	GUNJI ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-10 and 12-27 is/are pending in the application.
- 4a) Of the above claim(s) 14-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5-10,12,13,26 and 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 October 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

- [1]** Claims 1-2, 5-10, and 12-27 are pending in the application.
- [2]** Applicants' amendment to the claims, filed June 23, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.
- [3]** Claims 14-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.
- [4]** Claims 1-2, 5-10, 12-13, and 26-27 are being examined on the merits.
- [5]** Applicant's arguments filed June 23, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
- [6]** The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

- [7]** Claim 6 is objected to because of the following informalities: the term "said wherein said isolated strain" is grammatically incorrect and should be replaced with, for example, "wherein said isolated strain." Appropriate correction is required.

Claim Rejections - 35 USC § 101

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[8] In view of the amendment to the claims, the rejection of claims 1-8, 10-11, and 26-27 under 35 U.S.C. 101 as set forth in item [6] of the Office action mailed February 23, 2004, is withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

[9] In view of the amendment to the claims, the rejection of claim(s) 4-10 and 26-27 under 35 U.S.C. 112, second paragraph, as set forth in item [7] of the Office action mailed February 23, 2004, is withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

[10] The written description rejection of claims 1-2, 5-10, 12-13, and 26-27 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [8] of the Office action mailed February 23, 2004 and for the reasons stated below.

[11] RESPONSE TO ARGUMENTS: Applicants argue the claims have been amended to recite a specific bacterium, i.e., *Methylophilus methylotrophus* and that with this limitation, the representative species as disclosed in the specification support the claimed or recited genus. Applicants argue that not all members of the genus need be exemplified and the experimentation for determining other species encompassed by the genus is minimal and routine and is not undue. Applicants' argument is not found persuasive.

It is noted that, while the genus of enhanced bacteria is limited to a specific type of bacterium, i.e., a *M. methylotrophus* bacterium, there remains substantial variability

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within the genus regarding the structure and function of the L-amino acid biosynthetic enzyme(s) whose activity is enhanced (claims 1-2 and 12-13) or the structure(s) of the specific biosynthetic enzyme(s) whose activity is enhanced (claims 5-10 and 26-27) and the mechanism(s) by which this enzyme activity is enhanced. As such, the genus of claimed or recited M. methylotrophus bacteria encompasses WIDELY variant species. MPEP § 2163 states that when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the nine disclosed representative species (see page 5, line 17 to page 6, line 13 of the Office action mailed February 23, 2004) fail to represent the entire genus of claimed or recited M. methylotrophus bacteria, which encompasses species of M. methylotrophus bacteria having any L-amino acid biosynthetic enzyme(s) whose enzyme activity is enhanced (claims 1-2 and 12-13) or species of M. methylotrophus bacteria having any alteration within the structure(s) of the specifically recited biosynthetic enzyme(s) that results in enhanced enzyme activity (claims 5-10 and 26-27), wherein the enzyme activity is enhanced by any mechanism (claims 1-2, 5-8, 10, 12-13, and 26-27). Given the lack of description of a representative number of species of the claimed or recited genus of M. methylotrophus bacteria, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

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[12] The scope of enablement rejection of claim(s) 1-2, 5-10, 12-13, and 26-27 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record set forth in item [9] of the Office action mailed February 23, 2004 and for the reasons stated below.

[13] RESPONSE TO ARGUMENTS: Applicants argue the claims have been amended to recite a specific bacterium, i.e., M. methylotrophus and that with this limitation, the full scope of the claims is enabled as only routine experimentation is required to make the full scope of claimed or recited M. methylotrophus bacteria. Addressing the experimentation required, applicants argue methods of bacterial transformation, DNA expression, and measuring L-amino acid production are routine and that the genes and proteins that are altered are known in the prior art. Applicants argue that one of skill, having knowledge of the recited genes/proteins, the exemplified mutations thereof, and in view of the high level of skill in the art, would be able to make all M. methylotrophus bacteria encompassed within the scope of the claims. Applicants' argument is not found persuasive.

The examiner maintains the position that the specification, while being enabling for the nine disclosed working examples of M. methylotrophus (see page 5, line 17 to page 6, line 13 of the Office action mailed February 23, 2004), the specification fails to enable all M. methylotrophus broadly encompassed by the claims.

Even in light of the amendment to the claims to limit the bacteria to a M. methylotrophus bacterium, it is the examiner's position that the specification fails to enable the full scope of the claims. The claims are so broad as to encompass all M. methylotrophus bacteria having any L-amino acid biosynthetic enzyme(s) whose activity

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is enhanced by *any* mechanism(s) or all M. methylotrophus bacteria having any of the recited L-amino acid biosynthetic enzymes from any source – including mutants, variants, and those yet to be isolated – whose activity is enhanced by any mechanism(s). However, the specification fails to provide the guidance necessary for enabling this vast number of M. methylotrophus bacteria. While the specification provides nine working examples of the claimed or recited M. methylotrophus bacteria (see page 9, line 7 to page 10, line 5 of the Office action mailed February 23, 2004), there is no other specific guidance for generating a M. methylotrophus having an enhanced L-amino acid biosynthetic enzyme activity. As a result of the lack of guidance and working examples in the specification, there is a high degree of unpredictability in making the full scope of claimed or recited M. methylotrophus bacteria. Moreover, the claims are so broad as to encompass M. methylotrophus bacteria that have been altered to enhance L-amino acid biosynthetic enzyme activity by any method, including such random methods as UV mutagenesis and gene shuffling. One of skill recognizes the high level of unpredictability associated with randomly altering a bacterium with an expectation of obtaining a bacterium having the desired characteristics – particularly in view of the vast number of modifications of a M. methylotrophus bacterium that are encompassed by the claims. Further, the prior art recognizes a high level of unpredictability in making specific mutations to an encoding nucleic acid with an expectation of obtaining a nucleic acid encoding a protein having the desired characteristic, in this case, enhanced enzyme activity. For example, Branden et al. (“Introduction to Protein Structure”, Garland Publishing Inc., New York, 1991) teach

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"[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are exemplified by the reference of Witkowski et al. (*Biochemistry* 38:11643-11650) who teach that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Although methods of modifying the L-amino acid producing ability of a given bacteria are known, e.g., by transformation of the bacteria with a plasmid for overexpression of a desired enzyme, the experimentation required to make all M. methylotrophus bacteria encompassed by the scope of the claims is NOT routine.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of an M. methylotrophus bacterium having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[14] In view of the amendment to the claims, the rejection of claim(s) 1-3 and 11 under 35 U.S.C. 102(b) as being anticipated by Kim et al. as set forth in item [10] of the Office action mailed February 23, 2004 is withdrawn. Kim et al. neither teach nor suggest a M. methylotrophus bacterium having enhanced L-amino acid biosynthetic enzyme activity.

[15] Claim(s) 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Barth et al. (EP 0037273; cited by applicants in the IDS filed January 10, 2002) as evidenced by Voet et al. ("Biochemistry, 2nd Ed.," John Wiley and Sons, Inc., New York, 1995, pages 762-763). This rejection is necessitated by amendment. Claim 1 is drawn to an isolated strain of M. methylotrophus having L-amino acid producing ability, wherein L-amino acid biosynthetic enzyme activity is enhanced compared to a wild-type M. methylotrophus strain. Claim 2 limits the L-amino acid that the M. methylotrophus has the ability to produce.

The reference of Barth et al. teaches construction of an expression vector encoding murine dihydrofolate reductase (DHFR) and transformation of M. methylotrophus with the resulting expression vector (pages 8-10). The transformant was cultured and the cell extract analyzed for DHFR activity (pages 10-11). The cell extract of the M. methylotrophus transformant showed a significantly higher DHFR activity than the untransformed M. methylotrophus bacterium (page 11).

The reference of Voet et al. is relied upon to demonstrate that DHFR is an L-amino acid biosynthetic enzyme. Voet et al. teach DHFR catalyzes the conversion of

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dihydrofolate to tetrahydrofolate, which is an intermediate in the conversion of serine to glycine and histidine to glutamate (pages 762-763).

This anticipates claims 1-2 as written.

While it is noted that the reference of Barth et al. is silent as to M. methylotrophus bacterium having the ability to produce an L-amino acid, and more specifically those L-amino acids recited in claim 2, it is noted that this is an inherent feature of the M. methylotrophus bacterium as taught by Barth et al.

Claim Rejections - 35 USC § 103

[16] The rejection of claim(s) 1-2, 5-9, 12-13, and 26-27 under 35 U.S.C. 103(a) as being unpatentable over Kojima et al. in view of Barth et al., De Maeyer et al., and Kim et al. is maintained for the reasons of record as set forth in item [11] of the Office action mailed February 23, 2004 and for the reasons stated below.

[17] RESPONSE TO ARGUMENTS: Applicants argue that because it had been difficult to introduce mutations in methylotrophs by conventional methods used for mutating E. coli (citing Kim et al., page 105), this allegedly suggests that M. methylotrophus exhibits properties that are different from E. coli, including plasma membrane structure, metabolic pathways, and regulatory mechanisms. Applicants argue such differences are suggested by Tsygankov et al., which allegedly teaches mutants of M. flagellatum KT whose growth is inhibited in a medium that contains nutrients that are required for growth of E. coli. Applicants argue that because such phenomena had not been observed for E. coli, there is difficulty in modifying

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methylophs such as a M. methylotrophus bacterium. Applicants' argument is not found persuasive.

The teachings of Kim et al. show that a chemical mutagen, MNNG, which has the ability to diffuse across an E. coli cell membrane, does not diffuse across the cell membrane of a M. methylotrophus bacterium (page 107). The teachings of Tsygankov et al. show that *mutants* of M. flagellatum KT are inhibited in the presence of some amino acids and nucleotides. Although Kim et al. do point out a difference between E. coli and M. methylotrophus in the diffusion of a single compound, this in itself is not unusual as one of ordinary skill in the art would expect some differences between any two genera of bacteria. Further, the teachings of Tsygankov et al. are directed to *polyauxotrophic mutants* of M. flagellatum KT and are thus irrelevant to a comparison of recombinant DNA expression in E. coli and M. methylotrophus. Moreover, the cited references suggest using a wild-type strain of M. methylotrophus bacteria for recombinant protein expression, not the use of *polyauxotrophic mutants* of M. flagellatum KT for recombinant DNA expression and the examiner has made no suggestion that such mutants would be useful for recombinant DNA expression.

Based on applicants' evidence, one would not expect a M. methylotrophus bacterium to be refractory to modification by transformation of the bacterium with exogenous DNA or that the resulting transformant would not express the protein encoded by the exogenous DNA, particularly in view of the references of Barth et al. and De Maeyer et al., who demonstrate recombinant protein expression using M. methylotrophus as an expression host, showing that levels of recombinant protein

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expressed in E. coli and M. methylotrophus are equivalent or are *greater* in M. methylotrophus. Also, it is noted that Barth et al. and De Maeyer et al. teach culture conditions that resulted in successful recombinant protein expression using M. methylotrophus as a host cell. Thus, even assuming arguendo M. methylotrophus was not able to grow in a medium that supports growth of E. coli, in light of the guidance of Barth et al. and De Maeyer et al., one of ordinary skill would have chosen their conditions that resulted in successful recombinant protein expression using M. methylotrophus as an expression host. Thus, while the prior art may teach that there is difficulty in mutating M. methylotrophus using MNNG or that polyauxotrophic mutants of M. flagellatum KT do not grow under certain conditions, this evidence fails to teach away from using M. methylotrophus for recombinant protein expression, particularly for the biosynthesis of amino acids as is clearly suggested by Kim et al. Thus, in view of the combined teachings of the prior art, particularly the teachings of Barth et al. and De Maeyer et al., who teach using M. methylotrophus instead of E. coli for recombinant protein expression, the claimed M. methylotrophus bacterium and method of use thereof would have been obvious to one of ordinary skill in the art.

Applicants argue Barth et al. and De Maeyer et al. fail to cure the alleged deficiencies of Kojima et al. as their expressed proteins do not affect intracellular L-amino acid composition. Applicants argue that it was expected that upon introduction of a gene encoding an L-amino acid biosynthetic enzyme a M. methylotrophus bacterium might not grow as well due to an imbalance in intracellular L-amino acid composition. Applicants argue that one of ordinary skill in the art would be unable to obtain a strain of

M. methylotrophus which has an ability to produce L-amino acids based on the teachings of Barth et al. and De Maeyer et al., due to the unexpected result stated above. Applicants' argument is not found persuasive.

In response to applicants' argument that the proteins produced by Barth et al. and De Maeyer et al. in a M. methylotrophus bacterium do not affect intracellular L-amino acid composition, it should be noted that there is no requirement in the claims that the enzyme affect L-amino acid composition. It should also be noted that DHFR, whose overexpression in a M. methylotrophus host is taught by the reference of Barth et al., is considered to be an L-amino acid biosynthetic enzyme as DHFR reduces dihydrofolate to tetrahydrofolate, which is an intermediate in the conversion of serine to glycine and histidine to glutamate as evidenced by Voet et al. ("Biochemistry, 2nd Ed.," John Wiley and Sons, Inc., New York, 1995, pages 762-763).

In this case, Barth et al. and De Maeyer et al. clearly provide motivation for recombinantly expressing nucleic acids in a M. methylotrophus host cell rather than E. coli. Kim et al. explicitly state that methylotrophic bacteria have potential commercial value for producing amino acids and provide the example of M. methylotrophus as an example of such methylotrophic bacteria (page 105, left column). Thus, one of ordinary skill in the art would have recognized that a M. methylotrophus bacterium has the ability to produce amino acids. Moreover, there is no evidence of record that would indicate that the biochemical pathways of L-amino acid biosynthesis differ between M. methylotrophus and E. coli. In view of the teachings of the prior art, one of ordinary skill in the art would have been motivated to practice recombinant protein expression as

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taught by Kojima et al. with M. methylotrophus instead of E. coli and would have had a *reasonable* expectation of success for making the claimed M. methylotrophus and using this cell for L-amino acid production.

Applicants argue the reference of Kim et al. fails to make up for the deficiencies of Kojima et al. as it fails to demonstrate that L-amino acids had actually been produced by a strain of M. methylotrophus bacterium and only alludes to the potential commercial value of methylotrophic bacteria in general not a M. methylotrophus bacterium.

Applicants argue that such a mere mention fails to provide sufficient motivation and a reasonable expectation of success. Applicants' argument is not found persuasive.

In response to applicants' argument that Kim et al. fails to demonstrate that M. methylotrophus bacteria have the ability to produce L-amino acids, it is noted that L-amino acids are the necessary components of proteins, such as the proteins produced in the references of Barth et al. and De Maeyer et al. In order for such protein production to occur, L-amino acids must necessarily be produced and thus, one of ordinary skill in the art would clearly recognize that a M. methylotrophus bacterium has the ability to produce L-amino acids. Additionally, the teachings of Kim et al. clearly suggest that methylotrophic bacteria, which includes M. methylotrophus, have potential for commercial production of amino acids. As to applicants comment regarding M. methylotrophus and "progress in this area has been slow," it is noted that this statement in the reference of Kim et al. addresses the progress of creating mutant strains such as an auxotrophic strain, not progress in using methylotrophic bacteria for commercial purposes.

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In conclusion, it is the examiner's position that the cited references combine to make the claimed invention obvious to one of ordinary skill in the art at the time of the invention. The combination of the references teaches all limitations of the claims, provides motivation for substituting the host cell used in Kojima et al. with a M. methylotrophus host cell, and provides a reasonable expectation of success for the claimed M. methylotrophus bacterium and method of use thereof.

[18] The rejection of claim(s) 1-4, 7, 10, and 12-13 under 35 U.S.C. 103(a) as being unpatentable over Wang et al. in view of Barth et al., De Maeyer et al., and Kim et al. is maintained for the reasons of record as set forth in item [12] of the Office action mailed February 23, 2004 and for the reasons stated below.

[19] RESPONSE TO ARGUMENTS: Applicants argue the teachings of Wang et al. are similar to those of Kojima et al. with respect to using E. coli as a host cell and reiterate their arguments addressing the rejection under 35 USC 103(a) as stated above. Specifically, applicants reiterate their argument that the difficulties in modifying methylotrophic bacteria as compared to E. coli negate any expectation of success for modifying a M. methylotrophus bacterium in the same way as E. coli as in the reference of Wang et al. Applicants argue the references of Barth et al., De Maeyer et al., and Kim et al. fail to make up for the deficiencies of Wang et al., specifically addressing the mention of potential commercial value to methylotrophic bacteria failing to provide motivation to combine the references and that the combination does not provide a reasonable expectation of success. Applicants' argument is not found persuasive.

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The examiner maintains the position that the combined references make obvious the claimed M. methylotrophus bacterium and the method of use thereof at least for the reasons stated above. In view of the teachings of the combined references, one would have had motivation and a reasonable expectation of success for replacing the E. coli host cell of Wang et al. with a M. methylotrophus host cell, particularly in view of the advantages of using M. methylotrophus over E. coli and in view of the methods for successful recombinant protein expression using M. methylotrophus as an expression host as taught by Barth et al. and De Maeyer et al.

Double Patenting Rejection(s)

[20] In view of the amendment to the claims, the obviousness-type double patenting rejection of claims 1, 3-4, and 11-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of US Patent 6,350,596 ('596 Patent) as set forth in item [13] of the Office action mailed February 23, 2004, is withdrawn.

Conclusion

[21] Status of the claims:

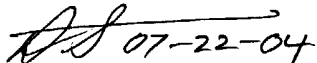
- Claims 1-2, 5-10, and 12-27 are pending.
- Claims 14-25 are withdrawn from consideration.
- Claims 1-2, 5-10, 12-13, and 26-27 are rejected.
- No claim is in condition for allowance.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

Handwritten signature of David J. Steadman, with the date 07-22-04 written below it.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652